Estrogen signaling in Kiss1 neurons promote strong bones in female mice.

SPOTLIGHT ON SCIENCE

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What is the main focus of your research?

Estrogen is the primary female sex hormone and has many different roles including critical roles in balancing energy allocation and expenditure to maximize reproductive fitness, reproduction and skeletal homeostasis. My research focuses on understanding how and why central estrogen signaling in the medial basal hypothalamus (MBH) of the brain controls energy allocation in a sex-dependent way. Trio RNA-seq was leveraged to better understand the mechanism of action on bone mass by characterizing the transcriptional changes in the bone marrow which occur after loss of central estrogen signaling in female mice. Our work has identified a previously unidentified role of central Estrogen Receptor Alpha (ERα) signaling on skeletal homeostasis. Remarkably, loss of ERα from the arcuate nucleus of the MBH results in a female-specific increase in bone mass. The increased bone mass persists with age and after removal of gonadal hormones by ovariectomy. Using different developmental Cre drivers we were able to identify Kisspeptin expressing neurons as the central regulators of the increased bone mass. Our data is the first to provide a link between fertility regulating neurons and bone mass.

Your recent paper identified a small neuronal population that regulates bone growth in female mice, what are the implications of this research?

Estrogen receptor alpha (ERα) is highly expressed in two distinct neuronal clusters in the medial basal hypothalamus (MBH), the arcuate nucleus (ARC) and the ventral lateral region of the ventromedial hypothalamus (VMHvl). Conditional deletion of ERα from the ARC but not the VMHvl resulted in increased bone mass in females but not males. RNA-Seq analysis of transcript changes in the ARC after loss of ERα identified two affected neuronal populations, Tyrosine hydoxyalse (TH) and Kisspeptin (Kiss1) expressing neurons. Using two different genetic Cre lines to developmentally delete ERα from TH or Kiss1 neurons we identified Kisspeptin neurons as key regulators of this brain to bone axis, linking fertility regulating neurons to skeletal homeostasis. Furthermore, our research suggests that these neurons regulate bone homeostasis sex-dependently.

The estrogen mediated brain-to-bone pathway has a strong phenotype only in female mice, do you suspect there is a similar testosterone mediated pathway in male mice?

We suspect that this brain to bone axis may be unique to females and maybe linked to female specific energy expenditure states such as pregnancy and lactation: two life phases which require estrogen signaling and skeletal remodeling. However, an estrogen sensitive brain to bone axis may exist in male mice and be regulated by another sexually dimorphic brain region.

What was the most challenging aspect of this research?

There were many challenging aspects to this research. One particular challenge was identifying the key neuronal subpopulation responsible for regulating bone mass. A second challenge was proving no compensatory increases in circulating gonadal hormones occurs after loss of hypothalamic ERα thereby disproving higher estrogen as the driving force behind the increased bone mass.

How has Trio RNA-Seq enabled this research?

Working with mice represents a challenge and any mistakes can cause months of delay and work to repeat the experiment. For this study, we microdissected the ARC tissue from control and mutant female mice which represents additional challenges due to limitations in RNA quantity and quality. In the past, we have used the Ovation RNA-Seq System V2 for these challenging samples. The Trio RNA-Seq kit provided a complete, streamlined workflow using the robust SPIA® (Single Primer Isothermal Amplification) technology with the added ability to removed rRNA using AnyDeplete™.

What is the long term goal of this work?

Understanding the role of central estrogen signaling in bone homeostasis can provide new targets for the treatment of age-related bone disease. Further research, however, is required and some long term goals of this work are to:

1) Understand how estrogen signaling in the brain regulates skeletal homeostasis.
2) Determine if there is a circulating factor released from the brain, which acts on the bone to induce growth.
3) which part of the brain to bone axis determines sex-dependency.
4) can this axis be identified in males and activated to increase bone density?

Publication

Estrogen Signaling in Arcuate Kiss1 Neurons Suppresses a Sex-Dependent Circuit That Promotes Dense Strong Bones in Female Mice

Candice B. Herber, William C. Krause, Liping Wang, James R. Bayrer, Alfred Li, Matthew Schmitz, Aaron Fields, Breanna Ford, Zhi Zhang, Michelle S. Reid, Daniel K. Nomura, Robert A. Nissenson, Stephanie M. Correa & Holly A. Ingraham

Nature Communications. 2019; , 2019, **10**, 163. doi:10.1038/s41467-018-08046-4

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V1.0, 2019-04

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